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Females with FVIII and FIX deficiency have reduced joint range of motion

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Abstract

Little is known about rates of joint bleeding among females with FVIII/FIX deficiency or hemophilia carriers. In a cross-sectional study, we tested the hypothesis that females with FVIII or FIX deficiency enrolled in the Universal Data Collection (UDC) project had a reduced mean overall joint range of motion (ROM) compared with historic controls from the Normal Joint Study. Demographics, clinical characteristics, and joint ROM measurements on 303 females without a bleeding disorder and 148 females with FVIII and FIX deficiency, respectively, between the ages of 2–69 years and a body mass index (BMI) ≤35 were compared. Multivariate linear regression was performed with the overall joint ROM (sum of the right and left ROM measurements of five joints) as the dependent variable and FVIII or FIX activity as the independent variable adjusting for age, race, BMI, and number of joint bleeds reported over the last 6 months. As FVIII and FIX activity decreased, the mean overall joint ROM became reduced and in most cases was significantly lower than that of the controls regardless of age and clinical hemophilia severity. Further investigation of reduced joint ROM as evidence of subclinical joint bleeding in females with FVIII and FIX deficiency is warranted.

Introduction

Hemophilia A and B are X-linked recessive disorders caused by mutations in the F8 and F9 genes, respectively, resulting in deficient residual factor activity with bleeding symptoms correlating to the severity of deficiency. Given the hemizygous nature of X-linked disorders,

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Author Contributions

Robert F. Sidonio designed the study and wrote the article. Fatima D. Mili performed statistical analyses and assisted in article writing. Tengguo Li assisted in article writing. Connie H. Miller, William C. Hooper, Michael R. DeBaun, and J. Michael Soucie contributed to study design and editing and revisions. J. Michael Soucie provided guidance in generation of the hypothesis, study design, and editing of the article.

mostly males are affected while females are more commonly heterozygous for the gene mutation, and are typically referred to as carriers. There are approximately 80,000 hemophilia carriers in the United States (U.S.) based on the premise that approximately 95% of mothers of males with hemophilia are carriers and there are at least four hemophilia carriers related to a single male with hemophilia [1]. Over the last decade, hemophilia carriers are increasingly using the Hemophilia Treatment Center (HTC) for their medical care. From 2002 to 2010, there was a 62% absolute rise in the number of hemophilia carriers being managed at HTCs [2]. The proportion of female patients receiving care at HTCs has grown to > 30% and hemophilia carriers are the second largest group after females with von Willebrand disease (VWD).

Hemophilia A and B carriers, even those with normal hemostatic levels (> 40%), might have an increased bleeding tendency, including but not limited to prolonged skin bleeding, heavy menstrual bleeding, oral bleeding and excessive bleeding following dental procedures, and surgery [3–5]. Joint bleeding is classically associated with males with hemophilia, and it has been self-reported by 8%–16% of hemophilia carriers [3,4]. Repeat bleeding into the joint can lead to chronic inflammation, ultimately leading to limited joint mobility, and reduced joint range of motion (ROM). Although joint bleeding contributes to the majority of morbidity in affected males, less is known about the prevalence of joint damage or destruction in hemophilia carriers. There are no studies to date evaluating joint abnormalities in hemophilia carriers and interrogation of the prevalence of reduced joint ROM, a possible surrogate for subclinical joint bleeding, has not been performed.

In response to the lack of a centralized dataset for persons with bleeding disorders, the Centers for Disease Control (CDC) created a national public health surveillance project called the Universal Data Collection (UDC) system. The UDC project was performed with the assistance of the federally funded HTCs in the United States, laypeople with bleeding disorders and the CDC. From 1998 to 2011, the HTC staff obtained informed consent from each UDC study participant and collected a standard set of clinical data as well as a plasma specimen for surveillance of potential blood-borne infections. Data collected included demographics, standardized joint range of motion, and limited bleeding and infectious disease history. The accuracy of the UDC project relies on the CDC infrastructure and oversight. This dataset has been maintained by the CDC and requires central review and revision of all proposals and data analysis before permission for submission for external publication.

Due to the lack of data on joint range of motion in healthy males and females across the life span, the CDC performed a cross-sectional study (Normal Joint Study) to establish normative joint range of motion data for comparison with persons with bleeding disorders [6]. Healthy males and females were recruited across multiple age groups (age 2–69), ethnicities, and BMI. Subjects with conditions that might limit joint range of motion were excluded including but not limited to anyone with Ehler Danlos Syndrome, BMI > 35, pregnancy, neurologic/rheumatologic disorders, and personal or a family history of a bleeding disorder. Measurements were collected by trained physical therapists using the same methods used for the UDC project.

To address the gap in knowledge between the high rate of self-reported joint bleeding and the perception that hemophilia carriers are clinically asymptomatic, we tested the hypothesis that females with FVIII or FIX deficiency enrolled in the Universal Data Collection (UDC) project had reduced joint ROM compared with historic controls from the Normal Joint Study [6].

Methods

Study design

We used a cross-sectional study design limiting analysis to female UDC participants age 2 years or older with FVIII or FIX deficiency. Females with FVIII or FIX deficiency were enrolled in the UDC by staff in one of the 136 federally funded HTCs in the United States. Participants with a BMI > 35 were excluded from the analysis because they were excluded from the control study; for participants with multiple visits, joint ROM data collected during the last comprehensive care visit were used. During the annual visit for the UDC study, participants had their height and weight measured in light clothing without shoes, and bilateral ROM measurements on five joints (hips, knees, shoulders, elbows, and ankles) were performed by a physical therapist or other trained health care provider according to detailed guidelines provided in a reference manual and training video (http://www.cdc.gov/ncbddd/video/jointrom/intro/) supplied by the Centers for Disease Control and Prevention (CDC). Participant body position for their joint measurements was standard and as follows: sitting for ankle dorsiflexion and plantarflexion and for elbow pronation and supination; supine for knee flexion, extension, and hyperextension, for hip flexion, for shoulder flexion, and for elbow flexion, extension, and hyperextension; and side lying for hip extension. Each joint was moved passively to its full extent, and end-point measurements were made to the nearest degree using a standard goniometer. The joints in which a bleed has occurred within 24 hrs or whose motion is restricted for another medical reason, such as an immobilization device or pregnancy (local determination made clinically if pregnant and unable to perform joint ROM), were not measured or included in the analysis. All health care providers performing these measurements were trained and certified by one of 12 regional physical therapists, who had previously received centralized training. Among the measured ROM data, 91% were collected by licensed physical therapists.

Demographic and clinical information was obtained from UDC study participants from the Hemophilia Treatment Centers Network during the annual care visit and was recorded using two standardized data collection forms. The forms were created to capture critical data on males with hemophilia. Females with FVIII or FIX deficiency were allowed to be included in the UDC dataset based on local physician preference. A registration form was completed at the time of enrollment for a new participant and included month and year of birth, age at first HTC visit, factor deficiency type (FVIII or FIX), and factor activity. Hemophilia severity was categorized as mild if the factor activity was > 5% and < 40%, moderate if ≥1% and 5% and severe if < 1% of normal. Additionally, females (presumed to be hemophilia carriers) with normal factor activity (≥40% and reported by the local HTC) were included in enrollment. Race and ethnicity were based on participant self-report and categorized in accordance with United States. census reporting. HTC staff used the annual visit form to

record current treatment and outcome data. HTC use by participants was categorized as frequent (one or more visits per year), infrequent (every 2–3 years), rare (visits every 4 or more years) or first visit according to the frequency of HTC visits during the previous annual period. If the participant infused clotting factor on a regular basis (e.g., two-three times a week) to prevent bleeding and the infusions were expected to continue indefinitely, she was considered to be on continuous prophylaxis treatment.

Female participants were assessed for the presence of neutralizing inhibitors based on local physician preference. Participants with an inhibitor titer of ≥1 Bethesda unit within a year before the annual comprehensive care visit were classified as having an inhibitor. Clinic and hospital records were reviewed by the local HTC to determine whether or not orthopedic surgery has been performed any joints during the previous year. Orthopedic surgical procedures were defined as arthrodesis, synovectomy, joint replacement, and other. None of the study participants reported orthopedic procedures thus all were included in analysis. Participants were asked to recall the total number of joint bleeds over the previous 6-month period during their annual visit.

Participants from The Normal Joint Study dataset [6] were used as controls for this study. This descriptive study determined measurements of female volunteers aged 2 to 69 years recruited in a variety of settings across the United States. Study exclusions comprised conditions that could potentially limit joint mobility, such as but not limited to BMI > 35, neurologic disorders impairing joint ROM, recent orthopedic injury, inability to ambulate without assistance, connective tissues disorder, a history of joint surgery, pregnancy, and waist to hip ratio > 1. Weight and height were measured in light clothing and BMI was calculated as weight in kilograms divided by the height in meters squared. Nine licensed physical therapists participated in a training session and were validated within < 5° in measurement. Joint ROM technique was identical to that used by licensed physical therapists and healthcare providers in the HTC Network.

Primary and secondary outcome assessment

The primary outcome was the mean overall joint ROM. The overall joint ROM was calculated for each female participant and was the sum of all flexion and extension (including hyperextension) measurements taken on all 10 joints in passive motion. Normal joint ROM values were derived from females in the Normal Joint Study. The sum of the overall joint ROM was used to calculate the mean overall joint ROM as the mean of all flexion and extension (including hyperextension) measurements for all females with FVIII or FIX deficiency from the UDC and for all normal females from the Normal Joint Study.

The secondary outcome was the joint ROM difference, defined as the difference between the sum of the mean overall joint ROM for females with FVIII or FIX deficiency and the sum of the mean overall joint ROM for normal females. Negative values for the joint ROM difference meant that affected females had reduced joint mobility relative to that of the healthy females.

Statistical analysis

Results were displayed as mean overall joint ROM with 95% confidence interval (CI) and P-values by age group and factor deficiency. Comparison of the mean overall joint ROM between females with FVIII or FIX deficiency and normal control females was assessed for statistical significance using the Wilcoxon-rank-sum test. The decision to analyze the females with FVIII separately from those with FIX deficiency was based on the a priori concern in discrepancy in bleeding phenotype. To account for potential confounders, multivariate linear regression was performed using the General Linear Model (GLM) procedure with the mean overall joint ROM as the dependent variable and the factor deficiency type and severity as the independent variable adjusting for race (white, non-white) and BMI (continuous). Confounding was assessed using a backward elimination strategy. Separate linear regression models were created stratifying by age (2–9, 10–19, 20–44, and 45–69 years) and hemophilia clinical severity (normal FVIII activity, mild, moderate, and severe FVIII deficiency). Hypothesis tests were two-tailed, and significance was based on achievement of a P-value < 0.05. All analyses were performed using SAS Version 9.3 statistical software (SAS Institute, Cary, NC).

Results

Demographic and clinical characteristics

Tables I and II present selected demographic and clinical characteristics of females with FVIII or FIX deficiency, respectively, who participated in the UDC between 1998 and 2010. A total of 670 females were enrolled in the UDC dataset. Of the 670 females identified with FVIII or FIX deficiency; 21% (144/670) of the females were removed because of lack of verification of factor deficiency type and 14% (75/526) of the females were removed due to being very obese (BMI > 35) or outside the age range studied in the Normal Joint Study. Descriptive statistics and joint ROM analysis were performed on 303 and 148 females with FVIII or FIX deficiency, respectively, between the ages of 2–69 years for comparison with the control group (Tables I and II). The majority of the females with FVIII or FIX deficiency were FVIII deficient (67%, 303/451), white (70% and 76%), and young adult age (median age of 25.5 and 23.5 years), respectively. In addition, 59% (147/249) and 61% (70/115) of the females with FVIII or FIX deficiency, respectively, were normal or underweight. The majority, 63% (158/249) and 61% (73/119), of females with FVIII or FIX deficiency, respectively, frequently used (visited their HTC at least every two years) their local HTC and 6% (15/249) and 4% (5/119) reported use of continuous factor prophylaxis, respectively. Finally, the percentage of females with FVIII deficiency reporting ≥1 joint bleed in the last 6 months before the annual visit increased as clinical severity worsened ranging from 0%, 15%, 36%, and 54% in normal, mild, moderate, and severe FVIII deficient states, respectively. A similar relationship was seen in females with FIX deficiency with 8%, 2%, 33%, and 37% reporting at least one joint bleed in normal, mild, moderate, and severe FIX deficient states, respectively.

When the joint ROM data in females with FVIII or FIX deficiency was stratified by whether the exam was performed by a licensed physical therapist or by some other trained health care provider, there was no significant difference in mean overall joint ROM. None of the

female participants reported undergoing immune tolerance therapy for inhibitor development, and none of the final evaluable participants were reported an orthopedic surgical procedure.

Joint ROM in females with FVIII deficiency

Table III summarizes the mean overall joint ROM among females with FVIII deficiency by age and factor activity. Females with FVIII deficiency had reduced joint ROM compared with controls. As FVIII activity decreased, the mean overall joint ROM became reduced and in most cases was significantly lower than that of the controls. There was a statistically significant reduction in mean overall joint ROM in all severities and age groups compared with participants in the Normal Joint Study, except in females 9–19 or 45–69 years of age with FVIII ≥1% and ≤5%, as well as in females 2–8 or 45–69 years with FVIII ≥40% (Table III). Using the joint ROM difference, loss of total joint ROM was noted in children as early as ages 2–8 years of age, becoming more limited with increasing clinical hemophilia severity (Table IV). There was a significant correlation between hemophilia severity and mean overall joint ROM in females with FVIII deficiency ($P < 0.0001$), except for females with moderate FVIII deficiency 45 years of age or older (Fig. 1). Multivariate analysis showed that females with FVIII activities of <1%, ≥1% and ≤5%, and >5% and <40% had a significantly reduced mean overall joint ROM compared with normal female controls, stratifying by age and clinical hemophilia severity and controlling for BMI and race (data not shown). In addition, the mean overall joint ROM was significantly lower in females with FVIII activities ≥1% and ≤5%, and <1% compared with females with FVIII activity ≥40%, adjusted for BMI, age, race, and joint bleeds over the last 6 months (data not shown).

Joint ROM in females with FIX deficiency

In females with FIX deficiency, we were limited on the depth of analysis that could be performed due to small sample size. Results indicated a statistically significant reduction in mean overall joint ROM in all severities and age groups compared with participants in the Normal Joint Study ($P < 0.0001$), except in females of all age groups with FIX ≥1% and ≤5%. As presented in Table V, the joint ROM difference was reduced compared with normal controls across age groups and clinical hemophilia severity, but the trend for loss of joint ROM was not linear. In addition, there was no statistically significant correlation between hemophilia severity and mean overall joint ROM.

Discussion

We were able to demonstrate that females with FVIII or FIX deficiency enrolled in the UDC project had a reduced mean joint ROM compared with historic controls from the Normal Joint Study. To our knowledge, this study is the first to report findings on joint abnormalities in females with FVIII or FIX deficiency and is the largest repository of females that are likely hemophilia carriers.

Our analyses suggested that subclinical joint bleeding might be occurring before adolescent years in both females with FVIII or FIX deficiency. If this is true, then further investigation

is warranted into the mechanism of reduction of ROM particularly as reduced joint ROM was seen with study participants with normal hemostatic activity (> 40%).

The rate of self-reported joint bleeds was high amongst FVIII and FIX deficient females. Our study demonstrates that a substantial number of females with mild and moderate FVIII and FIX deficiency reported at least one joint bleed within the previous 6-month period. Soucie et al [6] described > 40% of males with mild and moderate hemophilia self-reporting a joint bleed in the same time period, and approximately 35% of males with severe hemophilia reporting a joint bleed. The reason behind the discrepancy between severe and mild/moderate hemophiliacs reporting a joint bleed was the result of a higher percentage of use of factor prophylaxis. Regarding females with severe FVIII/FIX deficiency, we would expect a higher than reported percentage of females with severe FVIII or FIX deficiency to be on either primary or secondary factor prophylaxis. In the UDC cohort, only 25% and 27% of females with severe FVIII and FIX deficiency, respectively, reported the use of continuous factor prophylaxis. The reason for a small fraction of females with severe FVIII/FIX deficiency on factor prophylaxis might be due to multiple factors, including delayed identification of their disease due to their gender, and physician perception of reduced bleeding phenotype.

The extent of joint ROM reduction in females with FVIII or FIX deficiency, particularly those with mild deficiency, was unexpected. Soucie et al. [6] described that physiologic hypermobility, the ability to flex and extend beyond the established normal joint range, was lost by age 8, 8.6, and 12 years in males with severe, moderate, and mild hemophilia, respectively. Hypermobility was lost in all hemophilia severities in females by 8 years of age. The extent of reduction of joint ROM may be explained by the fact that females recruited for this study might have an increased bleeding tendency compared with the general population, as most hemophilia carriers are not routinely followed at HTCs, unless there is an increased bleeding tendency. In support of this notion, >60% of the females with FVIII or FIX deficiency recruited for the UDC study used their HTC frequently (Tables I and II) compared with >76% in males with FVIII or FIX deficiency [7]. Furthermore, the extent in reduction of joint ROM could also be the result of under-recognized early bleeding symptoms and late verification of hemophilia carrier status. We have demonstrated that the average age of identification of hemophilia carrier status was > 18 years of age in 78% (n = 47) of surveyed hemophilia carriers from a patient advocacy group [8].

In hemophilia A and B carriers, the mean FVIII level is ~50% of the normal mean, or one half of the expected value for a group of non-carrier women, potentially putting women at increased bleeding risk. There is a likely continuum of bleeding phenotypes starting within the low end of the normal range and extending into the abnormal [9]. In females with FVIII deficiency, it should be noted that FVIII activity increases with age, and the levels of this cohort may have been low enough when they were younger to put them at greater risk of joint bleeding compared to in life.

This study has, however, several limitations. First, females with FVIII or FIX deficiency were enrolled based on local physician preference. It is unknown what the motivators of the local physician were in consideration of enrollment of hemophilia carriers into the UDC

study. Because not all the HTCs enrolled females with FVIII or FIX deficiency, there is likely selection bias. We were not able to determine whether the analyzed cohort was different compared with females with FVIII or FIX deficiency that do not receive care in HTCs. As it is likely that mostly symptomatic females with FVIII or FIX deficiency were enrolled in the UDC, one would expect a slightly higher than expected reduction in mean overall joint ROM. However, this study reports joint abnormalities in this population and it is consistent with the self-reported joint bleeding rate of 8%–16% in previous studies [3,4]. Second, this study lacked universal genetic verification of hemophilia carrier status (FVIII or FIX deficiency). In this UDC cohort, 17% of all the females identified were genetically verified as carriers of hemophilia, while more than 33% of the females with severe FVIII or FIX deficiency were genetically confirmed. It is highly likely that those enrolled were carriers of hemophilia. Due to privacy protection and wide HTC distribution of the participants, however, we were not able to link the UDC data of the patients to those of their male relatives. During quality control evaluation of the data, we found none of the females with FVIII or FIX deficiency had VWD listed as a diagnosis, and all of reported factor activities correlated with hemophilia clinical severity classification.

In summary, females with FVIII or FIX deficiency had evidence of reduced overall joint ROM noted as early as the pre-teen years. This study is the first step in demonstrating that subclinical or asymptomatic joint damage occurs in females with FVIII or FIX deficiency regardless of the hemophilia clinical severity. Investigation into whether these joint abnormalities correlate with magnetic resonance imaging changes is underway.

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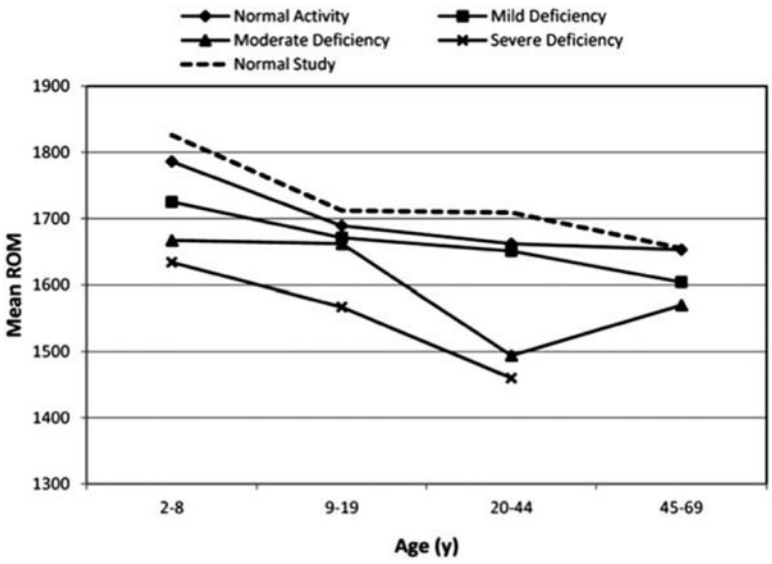

Figure 1.

Predicted mean overall range of motion (ROM) by age and clinical severity, for 2- to 69-year old females with FVIII deficiency. Graph was created using separate linear regression models for normal FVIII activity, and for mild, moderate, and severe FVIII deficiency adjusted for race and body mass index (BMI). Mean overall ROM was calculated by setting categorical variables equal to the reference value and by using the severity group mean for the continuous variable BMI. Normal activity (>40% FVIII); Mild deficiency (>5%–40%); Moderate deficiency (1%–5%); Normal Study (normal females from Normal Joint Study).

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TABLE I

Characteristics of Females With FVIII Deficiency who Participated in the UDC 1998–2010

FVIII severity	**≥ 40% (Normal)**	**>5% to <40% (Mild)**	**≥ 1% to ≤5% (Moderate)**	**<1%[a] (Severe)**	***P* value[b]**
Age (years)	*n* = 41	*n* = 212	*n* = 20	*n* = 30	0.08
2–8	15%	16%	30%	33%	
9–19	27%	26%	10%	20%	
20–44	53%	43%	40%	47%	
45–69	5%	15%	20%	0%	
Race/ethnicity	*n* = 41	*n* = 212	*n* = 20	*n* = 30	0.04
White	61%	75%	70%	44%	
Hispanic	7%	15%	15%	13%	
Black	2%	6%	5%	13%	
Asian/Pacific Islander	15%	1%	10%	13%	
Native American	12%	1%	0%	0%	
Other	2%	2%	0%	17%	
BMI[c]	*n* = 33	*n* = 176	*n* = 14	*n* = 26	0.06
<18.5	19%	15%	36%	35%	
8.5–24.99	42%	41%	43%	35%	
25–29.99	27%	25%	7%	23%	
30–35	12%	19%	14%	7%	
HTC usage	*n* = 33	*n* = 176	*n* = 14	*n* = 26	0.16
Frequent	64%	60%	86%	76%	
Infrequent	18%	24%	7%	12%	
Rare or first visit	18%	16%	7%	12%	
Prophylaxis use[d]	*n* = 33	*n* = 176	*n* = 14	*n* = 26	<0.0001
Yes	6%	2%	21%	27%	
Number of joint bleeds in last 6 months	*n* = 31	*n* = 176	*n* = 14	*n* = 24	<0.0001
0	100%	85%	64%	46%	
1–4	0%	13%	22%	33%	
5+	0%	2%	14%	21%	

[a]Two females with severe FVIII deficiency with inhibitor with 1 BU.

[b] Mantel-Haenszel Chi-Square test *P* values for the differences in distributions of characteristics across the clinical severity categories.

[c] Excludes obese women (BMI > 35).

[d] Prophylaxis defined as continuous prophylactic factor replacement excluding intermittent use.

TABLE II

Characteristics of Females With FIX Deficiency who Participated in the UDC 1998–2010

FIX severity	≥40% (Normal)	>5% to <40% (Mild)	≥1% to ≤5% (Moderate)	<1% (Severe)	*P* value[a]
Age (years)	*n* = 17	*n* = 109	*n* = 11	*n* = 11	0.58
2–8	29%	19%	55%	36%	
9–19	47%	31%	1%	18%	
20–44	12%	33%	17%	46%	
45–69	12%	17%	17%	0%	
Race/ethnicity	*n* = 17	*n* = 109	*n* = 11	*n* = 11	0.61
White	82%	72%	100%	73%	
Hispanic	0%	14%	0%	9%	
Black	12%	9%	0%	0%	
Asian/Pacific Islander	0%	1%	0%	0%	
Native American	0%	1%	0%	0%	
Other	6%	3%	0%	18%	
BMI[b]	*n* = 13	*n* = 86	*n* = 8	*n* = 8	0.55
<18.5	23%	19%	37%	26%	
18.5–24.99	31%	41%	25%	37%	
25–29.99	38%	30%	25%	37%	
30–35	8%	10%	13%	0%	
HTC usage	*n* = 14	*n* = 88	*n* = 9	*n* = 8	0.84
Frequent	43%	60%	67%	62%	
Infrequent	36%	22%	11%	25%	
Rare or first visit	21%	18%	22%	13%	
Prophylaxis use[c]	*n* = 14	*n* = 88	*n* = 9	*n* = 8	0.002
Yes	0%	2%	11%	25%	
Number of joint bleeds in last 6 months	*n* = 13	*n* = 66	*n* = 9	*n* = 8	0.015
0	92%	98%	67%	63%	
1–4	8%	2%	33%	37%	
5+	0%	0%	0%	0%	

[a] Mantel-Haenszel Chi-Square test *P* values for the differences in distributions of characteristics across the clinical severity categories.

[b] Excludes obese women (BMI >35).

[c] Prophylaxis defined as continuous prophylactic factor replacement excluding intermittent use.

TABLE III

Mean Overall Joint Range of Motion (ROM) Among Females[a] with FVIII Deficiency by Age and Factor Activity

Age (years)	*n*	Normal joint study (Mean ROM) (95% CI)	*n*	FVIII ≥40% (Mean ROM) (95% CI)[b]	*n*	FVIII >5% and <40% (Mean ROM) (95% CI)[b]	*n*	FVIII ≥1% and ≤	*n*	FVIII <1% (Mean ROM) (95% CI)[b]
2 to 8	39	1878 (1856–1890)	6	1786 (1674–1897) *P* = 0.09	34	1725 (1683–1767) *P* < 0.0001	6	1667 (1575–1759) *P* = 0.0002	10	1634 (1591–1677) *P* < 0.0001
9 to 19	56	1753 (1736–1769)	11	1685 (1639–1732) *P* = 0.005	55	1687 (1661–1714) *P* < 0.0001	2	1663 (939–2387) *P* = 0.09	6	1597 (1439–1755) *P* = 0.004
20 to 44	143	1745 (1734–1755)	22	1662 (1583–1741) *P* = 0.01	91	1650 (1625–1674) *P* < 0.0001	8	1494 (1313–1675) *P* = 0.0002	14	1463 (1341–1584) *P* < 0.0001
45 to 69	123	1688 (1677–1700)	2	1653	32	1603 (1543–1664) *P* < 0.0001	4	1570	–	–

[a] Excludes obese women (BMI >35).

[b] Wilcoxon-rank-sum test *P* values for the differences in mean overall joint ROM between females with FVIII deficiency and normal females.

TABLE IV

Range of Motion (ROM) Difference Among Females[a] with FVIII Deficiency by Age and Factor Activity

Age (years)	*n*	FVIII ≥40% (ROM difference)	*n*	FVIII >5% and <40% (ROM difference)	*n*	FVIII ≥1% and ≤5% (ROM difference)	*n*	FVIII <1% (ROM difference)
2 to 8	6	−92.1°	34	−148.6°	6	−193.1°	10	−224.8°
9 to 19	11	−68.2°	55	−70.3°	2	−73.9°	6	−148.9°
20 to 44	22	−52.2°	91	−94.7°	8	−246.1°	14	−277.4°
45 to 69	2	−62.0°	32	−79.1°	4	−111.0°	–	–

[a]Excludes obese women (BMI >35).

TABLE V

Range of Motion (ROM) Difference Among Females[a] with FIX Deficiency by Age and Factor Activity

Age (years)	*n*	FIX ≥ 40% (ROM difference)	*n*	FIX >5% and <40% (ROM difference)	*n*	FIX ≥1% and ≤5% (ROM difference)	*n*	FIX <1% (ROM difference)
2–8	5	−200.4°	21	−172.8°	6	−108.4°	4	−123.6°
9–19	8	−132.3°	34	−60.6°	1	37.1°	2	−84.4°
20–44	2	−178.2°	36	−73.2°	2	–	5	−100.0°
45–69	2	−20.0°	18	−57.4°	2	−30.0°	–	–

[a]Excludes obese women (BMI > 35).